Atty. Docket No.: Le A 34 491

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Lerchen, *et al.*

SERIAL NO.: New filing

FILING DATE: herewith

TITLE: Cytostatic-Glycoconjugates Having Specifically Cleavable Linking Units

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PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Preliminary Amendment is submitted in the above-captioned application. Please amend the application as follows:

In the Claims

Please cancel claims 8 and 10.

Please amend claims 1-7 and 9, as shown in the attached sheets. A marked version of the claim set showing the changes made is also attached.

Please add new claims 11-26, as shown in the attached sheet.

Remarks

By way of this Preliminary Amendment, claims 1-7, 9, and 11-26 are pending. Claims 8 and 10 have been cancelled, and claims 1-7 and 9 have been amended. New claims 11-26 has been added. These claim cancellations, amendments, and additions are being made solely for purposes of placing the claims in a format appropriate for U.S. prosecution. Applicants submit that the amendments do not change the scope of the claims as originally filed. Such amendments are therefore made to address formalities in the claim format and are not related to the patentability of the subject matter of the claims. No new matter was added by way of these claim amendments and additions.

Conclusion

Applicants believe that the subject matter of the pending claims is patentable and that the instant application should accordingly be allowed. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned attorney at (203) 812-6450.

Respectfully submitted,

Dated: December 20, 2001

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Amended Claims (Attorney Docket No. Le A 34 491)

1. (Amended) A conjugate, characterized by the formula (I)

$$CT - LI - Sp1 - Sp2 - K \qquad (I)$$

in which

CT denotes a cytotoxic radical or a radical of a cytostatic or of a cytostatic derivative, which can additionally carry a hydroxyl, carboxyl or amino group,

LI is a linker group comprising 5 to 8 amino acid residues in the D or L configuration, which can each optionally carry protective groups,

Sp1 is absent or a carbonyl or a thiocarbonyl radical,

Sp2 is an optionally substituted arylene or alkylene radical,

K is an unsubstituted or regioselectively modified carbohydrate radical;

and their physiologically acceptable salts, hydrates and stereoisomers.

2. (Amended) The conjugate according to Claim 1, characterized in that

LI is a linker group having the formula

-AA1-AA2-AA3-AA4-AA5-AA6-AA7-AA8-

wherein at least 5 of the radicals AA1 to AA8 are present, AA1 is bonded to the radical CT and

AA1 is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, glutamate, aspartate, serine, lysine, ornithine and phenylalanine;

AA2 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, valine, phenylalanine, tyrosine, threonine, serine, isoleucine, lysine, glutamate, histidine, glycine, arginine, asparagine, glutamine, S-methyl-cysteine, methionine, arginine, aspartate, tryptophane, proline, ornithine and leucine, and can optionally carry protective groups,

AA3 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, valine, phenylalanine, tyrosine, serine, isoleucine, lysine, glutamate, histidine, glycine, arginine, aspartate, tryptophane, proline, ornithine, methionine, S-methyl-cysteine, norvaline and leucine, and can optionally carry protective groups,

AA4 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, cysteine and norvaline;

AA5 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, tyrosine, glutamine, asparagine, proline, methionine, phenylalanine and cysteine;

AA6 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, glutamine, asparagine, aspartate and proline;

AA7 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, γ-aminobutyric acid, aspartate, glutamate, lysine and proline;

AA8 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, lysine, proline and γ-aminobutyric acid;

and the other radicals CT, Sp1, Sp2 and K are as defined in claim 1.

3. (Amended) The conjugate according to claim 2, characterized in that

LI is a linker group having the formula

-AA1-AA2-AA3-AA4-AA5-AA6-AA7-AA8-

wherein 5 to 7 of the radicals AA1 to AA8 are present, AA1 is bonded to the radical CT and

AA1 is valine, glycine, leucine, histidine;

AA2 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine,

phenylalanine, serine, isoleucine, glutamate, asparagine, glutamine, histidine, glycine, aspartate, tryptophane, proline, and leucine, and can optionally carry protective groups,

AA3 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, phenylalanine, serine, isoleucine, norvaline, S-methylcysteine, methionine, glutamate, histidine, glycine, aspartate, tryptophane, and leucine, and can optinally carry protective groups,

AA4 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, leucine, cysteine and norvaline, and can optionally carry protective groups,

AA5 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, histidine, glutamine, phenylalanine, isoleucine, and methionine,

AA6 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, proline, glutamine, methionine, and leucine;

AA7 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, leucine, aspartate, histidine, γ-aminobutyric acid and proline;

AA8 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, proline and γ-aminobutyric acid ;

and the other radicals CT, Sp1, Sp2 and K are as defined in claim 1.

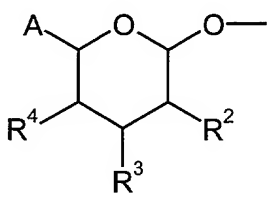
4. (Amended) The conjugate according to claim 2 or 3, characterized in that

CT is camptothecin or a camptothecin derivative, which can be bonded to the rest of the conjugate via the C20-OH group,

LI is as defined in claim 2 or 3, respectively;

Sp is absent, or is a carbonyl or a thiocarbonyl radical,

K is a carbohydrate moeity of the formula (II)



(II)

wherein

A is methyl, hydroxymethyl, carboxy and esters und amides derived therefrom, alkoxymethyl, acyloxymethyl oder carboxyalkyloxymethyl and esters und amides derived therefrom, or CH_2-B,

wherein

B is also a carbohydrate radical of the formula (II) which is bonded via its anomeric centre;

R^2, R^3 and R^4 are identical or different from each other and denote H, hydroxy, alkyloxy, carboxyalkyloxy and esters und amides derived therefrom, hydroxyalkyloxy, aminoalkyloxy, acyloxy, carboxyalkylcarbonyloxy, sulfato, phosphato, halogen, or a modified carbohydrate radical of the formula (II) which is bonded via its anomeric centre, wherein R2 additionally can denote amino or acylamino, and/or wherein two of the radicals R^2, R^3 and R^4 together can form an epoxy moiety.

5. (Amended) The conjugate according to Claim 2 or 3, characterized in that

Sp2 is arylene which is substituted in ortho, meta or para position with K and Sp1 and can additionally carry 1 to 4 further radicals which are identical or different from each other and are selected from the group consisting of H, methyl, methoxy, hydroxy, carboxy, methyloxycarbonyl, cyano, nitro, halogen, sulfonyl oder sulfonamide,

or is a linear or branched alkylene radical,

and the other radicals CT, LI, Sp1 and K are as defined in claim 2 or 3.

6. (Amended) The conjugate according to claim 1, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 1.

7. (Amended) A process for the preparation of conjugates according to Claim 1, comprising

the reaction of a compound of the formula (III)

$$K\text{-}Sp2\text{-}NH_2 \qquad (III)$$

wherein K and Sp2 are as defined in claim 1,

with a carbonic acid derivative such as, for example, phosgene, thiophosgene or a chloroformic acid ester, if appropriate in the presence of a base,

followed by the reaction with a compound of the formula (IV) which has a free primary or secondary amino group

$$CT\text{-}LI \qquad (IV)$$

wherein CT and LI are as defined in claim 1,

and

if appropriate the removal of protective groups and/or derivatization of nitrogen atoms present at preferred points of time in the preparation process and/or conversion of the compound obtained into the free acid and/or conversion of the compound obtained into one of its physiological salts by reaction with an inorganic or organic base or acid.

8. Cancelled.

9. (Amended) A pharmaceutical composition comprising at least one of the compounds according to any of Claims 1 to 6.

10. Cancelled.

11. (New) The conjugate according to claim 2, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 2.

12. (New) The conjugate according to claim 3, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 3.

13. (New) The conjugate according to claim 4, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 4.

14. (New) The conjugate according to claim 5, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 5.

15. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 1.

16. (New) The method of claim 15, wherein the disease is carcinomatous disorders.

17. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 2.

18. (New) The method of claim 17, wherein the disease is carcinomatous disorders.

19. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 3.

20. (New) The method of claim 19, wherein the disease is carcinomatous disorders.

21. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 4.

22. (New) The method of claim 21, wherein the disease is carcinomatous disorders.

23. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 5.

24. (New) The method of claim 23, wherein the disease is carcinomatous disorders.

25. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 6.

26. (New) The method of claim 25, wherein the disease is carcinomatous disorders.

Amended Claims (Attorney Docket No. Le A 34 491)
Version with Markings to Show Changes to Claims

1. (Amended) A conjugate, characterized by the formula (I)

$$CT - LI - Sp1 - Sp2 - K \qquad (I)$$

in which

CT denotes a cytotoxic radical or a radical of a cytostatic or of a cytostatic derivative, which can additionally carry a hydroxyl, carboxyl or amino group,

LI is a linker group comprising 5 to 8 amino acid residues in the D or L configuration, which can each optionally carry protective groups,

Sp1 is absent or a carbonyl or a thiocarbonyl radical,

Sp2 is an optionally substituted arylene or alkylene radical,

K is an unsubstituted or regioselectively modified carbohydrate radical;

and their physiologically acceptable salts, hydrates and stereoisomers.

2. (Amended) The conjugate according to Claim 1, characterized in that

LI is a linker group having the formula

-AA1-AA2-AA3-AA4-AA5-AA6-AA7-AA8-

wherein at least 5 of the radicals AA1 to AA8 are present, AA1 is bonded to the radical CT and

AA1 is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, glutamate, aspartate, serine, lysine, ornithine and phenylalanine;

AA2 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, valine, phenylalanine, tyrosine, threonine, serine, isoleucine, lysine, glutamate, histidine, glycine, arginine, asparagine, glutamine, S-methyl-cysteine, methionine, arginine, aspartate, tryptophane, proline, ornithine and leucine, and can optionally carry protective groups,

AA3 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, valine, phenylalanine, tyrosine, serine, isoleucine, lysine, glutamate, histidine, glycine, arginine, aspartate, tryptophane, proline, ornithine, methionine, S-methyl-cysteine, norvaline and leucine, and can optionally carry protective groups,

AA4 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, cysteine and norvaline;

AA5 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, tyrosine, glutamine, asparagine, proline, methionine, phenylalanine and cysteine;

AA6 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, glutamine, asparagine, aspartate and proline;

AA7 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, γ-aminobutyric acid, aspartate, glutamate, lysine and proline;

AA8 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, histidine, lysine, proline and γ-aminobutyric acid;

and the other radicals CT, Sp1, Sp2 and K are as defined in claim 1.

3. (Amended) The conjugate according to claim 2, characterized in that

LI is a linker group having the formula

-AA1-AA2-AA3-AA4-AA5-AA6-AA7-AA8-

wherein 5 to 7 of the radicals AA1 to AA8 are present, AA1 is bonded to the radical CT and

AA1 is valine, glycine, leucine, histidine;

AA2 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine,

phenylalanine, serine, isoleucine, glutamate, asparagine, glutamine, histidine, glycine, aspartate, tryptophane, proline, and leucine, and can optionally carry protective groups,

AA3 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of alanine, phenylalanine, serine, isoleucine, norvaline, S-methylcysteine, methionine, glutamate, histidine, glycine, aspartate, tryptophane, and leucine, and can optinally carry protective groups,

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AA6 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, proline, glutamine, methionine, and leucine;

AA7 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, leucine, aspartate, histidine, γ-aminobutyric acid and proline;

AA8 is absent or is a naturally occurring amino acid in the D or L configuration, which is selected from the group consisting of glycine, proline and γ-aminobutyric acid ;

and the other radicals CT, Sp1, Sp2 and K are as defined in claim 1.

4. (Amended) The conjugate according to claim 2 or 3, characterized in that

CT is camptothecin or a camptothecin derivative, which can be bonded to the rest of the conjugate via the C20-OH group,

LI is as defined in claim 2 or 3, respectively;

Sp is absent, or is a carbonyl or a thiocarbonyl radical,

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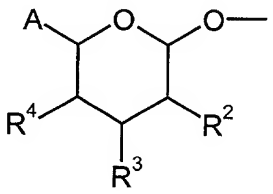

(II)

wherein

A is methyl, hydroxymethyl, carboxy and esters und amides derived therefrom, alkoxymethyl, acyloxymethyl oder carboxyalkyloxymethyl and esters und amides derived therefrom, or CH_2-B,

wherein

B is also a carbohydrate radical of the formula (II) which is bonded via its anomeric centre;

R^2, R^3 and R^4 are identical or different from each other and denote H, hydroxy, alkyloxy, carboxyalkyloxy and esters und amides derived therefrom, hydroxyalkyloxy, aminoalkyloxy, acyloxy, carboxyalkylcarbonyloxy, sulfato, phosphato, halogen, or a modified carbohydrate radical of the formula (II) which is bonded via its anomeric centre, wherein R2 additionally can denote amino or acylamino, and/or wherein two of the radicals R^2, R^3 and R^4 together can form an epoxy moiety.

5. (Amended) The conjugate according to Claim 2 or 3, characterized in that

Sp2 is arylene which is substituted in ortho, meta or para position with K and Sp1 and can additionally carry 1 to 4 further radicals which are identical or different from each other and are selected from the group consisting of H, methyl, methoxy, hydroxy, carboxy, methyloxycarbonyl, cyano, nitro, halogen, sulfonyl oder sulfonamide,

or is a linear or branched alkylene radical,

and the other radicals CT, LI, Sp1 and K are as defined in claim 2 or 3.

6. (Amended) The conjugate according to [any of the] claim[s] 1 [to 5], further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim[s] 1 [to 5].

7. (Amended) A process for the preparation of conjugates according to Claim 1, comprising

the reaction of a compound of the formula (III)

$$K\text{-}Sp2\text{-}NH_2 \qquad (III)$$

wherein K and Sp2 are as defined in claim 1,

with a carbonic acid derivative such as, for example, phosgene, thiophosgene or a chloroformic acid ester, if appropriate in the presence of a base,

followed by the reaction with a compound of the formula (IV) which has a free primary or secondary amino group

$$CT\text{-}LI \qquad (IV)$$

wherein CT and LI are as defined in claim 1,

and

if appropriate the removal of protective groups and/or derivatization of nitrogen atoms present at preferred points of time in the preparation process and/or conversion of the compound obtained into the free acid and/or conversion of the compound obtained into one of its physiological salts by reaction with an inorganic or organic base or acid.

8. Cancelled.

9. (Amended) A pharmaceutical composition [Medicament,] comprising at least one of the compounds according to any [one] of Claims 1 to 6.

10. Cancelled.

11. (New) The conjugate according to claim 2, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 2.

12. (New) The conjugate according to claim 3, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 3.

13. (New) The conjugate according to claim 4, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 4.

14. (New) The conjugate according to claim 5, further characterized in that

CT is camptothecin, which can be linked to the rest of the conjugate via the C20-OH group;

and the other radicals LI, Sp1, Sp2, and K are as defined in claim 5.

15. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 1.

16. (New) The method of claim 15, wherein the disease is carcinomatous disorders.

17. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 2.

18. (New) The method of claim 17, wherein the disease is carcinomatous disorders.

19. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 3.

20. (New) The method of claim 19, wherein the disease is carcinomatous disorders.

21. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 4.

22. (New) The method of claim 21, wherein the disease is carcinomatous disorders.

23. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 5.

24. (New) The method of claim 23, wherein the disease is carcinomatous disorders.

25. (New) A method of treating a disease comprising administering an effective amount of a compound of claim 6.

26. (New) The method of claim 25, wherein the disease is carcinomatous disorders.